Electrostatic vs. Orbital Control of Facial Selectivities in π Systems: Experimental and Theoretical Study of Electrophilic Additions to 7-Isopropylidenenorbornanes**

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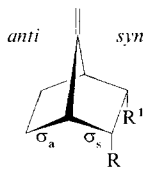
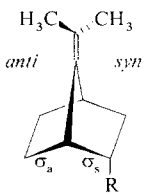
Dedicated to Professor C. N. R. Rao on the occasion of his 60th birthday

Evaluation of the relative importance of electrostatic and orbital effects in determining facial selectivities of π systems (π-facial selectivity) in nucleophilic and electrophilic additions to trigonal carbon centers is currently a topic of intense debate.[1–3] We have recently reported[2] the addition of electrophiles such as BH_3, peracid, and $Hg(OAc)_2$ to some *endo*-substituted 7-methylenenorbornanes, for example **1a**, with sterically indistinguishable π faces and reconciled the observed *syn*-face selectivity in terms of the Cieplak model,[4] according to which the electrophiles should approach **1a** from the face opposite to the more electron-rich σ_a bond. However, on the basis of PM3 calculations on 7-methylenenorbornyl derivatives **1a**, **1c**, and related systems, it has been proposed[3] that the initial approach of a charged reagent would be along the *anti* side, governed by electrostatics, and the subsequent nucleophilic attack (for example, by water) would lead to the observed product stereochemistry.



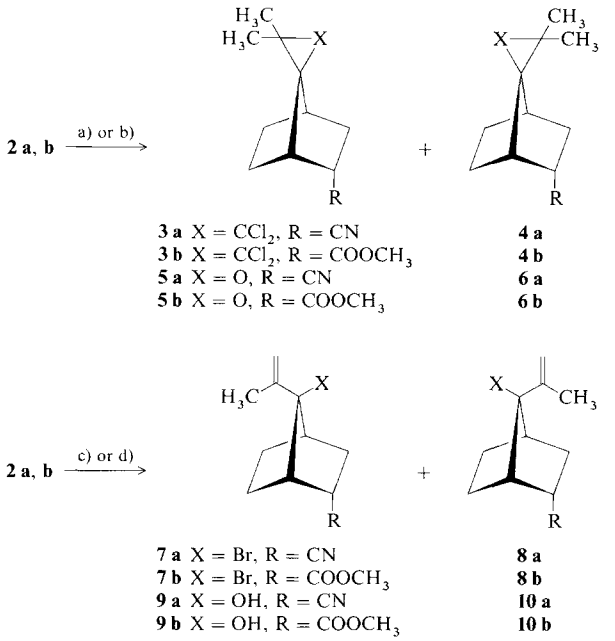
1a R = R¹ = $COOCH_3$
1b R = F, R¹ = H
1c R = R¹ = F
1d R = CN, R¹ = H
1e R = R¹ = CN

Studies on CCl_2 and halonium ion additions to these systems were suggested for providing further insights. We now report experimental facial selectivities for the addition of such electrophiles to 7-isopropylidenenorbornane derivatives (**2**) and provide interpretations on the basis of ab initio molecular electrostatic potentials (MEP) and electron densities, as well as semiempirical transition state energetics. The use of the isopropylidene unit offers significant advantages. From an experimental point of view, the double bond becomes more reactive, which enables the study of carbene additions.[5] Further, unlike in **1**, the site of electrophilic attack is likely to be at C7 and not at C8, a factor which is crucial for interpretation of the experimental results. Finally, the mechanistic details of electrophilic attack in **2** are unambiguous and the steric neutrality on the two π faces is maintained.



2a R = CN
2b R = $COOCH_3$

7-Isopropylidenenorbornanes **2** smoothly undergo dichlorocarbene and singlet oxygen addition, epoxidation, and reaction with the bromine(I) cation. The reaction conditions, yields, and products obtained are shown in Scheme 1, and the π-face selectivities are summarized in Table 1. Structures of diastereomers were determined on the basis of ^1H and ^{13}C NMR data, but more specifically through the greater deshielding of the C_2 *exo*-proton in the *syn*-addition products (**3**, **5**, **7**, **9**) relative to that of the *anti*-products (**4**, **6**, **8**, **10**).[2, 6, 7]



3a X = CCl_2, R = CN — **4a**
3b X = CCl_2, R = $COOCH_3$ — **4b**
5a X = O, R = CN — **6a**
5b X = O, R = $COOCH_3$ — **6b**

7a X = Br, R = CN — **8a**
7b X = Br, R = $COOCH_3$ — **8b**
9a X = OH, R = CN — **10a**
9b X = OH, R = $COOCH_3$ — **10b**

Scheme 1. Electrophilic additions to **2**. a) $Cl_3CCOO^-Na^+$, dimethoxyethane (DME)/tetrachloroethylene, Δ, 80–93%; b) *m*-chloroperbenzoic acid (*m*-CPBA), Na_2CO_3, CH_2Cl_2, 0–5 °C, 90–95%; c) *N*-bromosuccinimide, 10% aqueous DME, 95%; d) $^1O_2$, *hv*, methylene blue, CH_2Cl_2, then $NaBH_4$, MeOH, 75–81%.

Table 1. Experimental ratios of *syn*- and *anti*-addition products of **2** with $:CCl_2$, *m*-CPBA, Br^+, and $^1O_2$ [a].

Compound	$:CCl_2$		*m*-CPBA		Br^+		$^1O_2$	
	syn	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*	*anti*
2a	78	22	77	23	72	28	78	22
	3a	**4a**	**5a**	**6a**	**7a** [b]	**8a** [b]	**9a**	**10a**
2b	60	40	62	38	59	41	61	39
	3b	**4b**	**5b**	**6b**	**7b** [b]	**8b** [b, c]	**9b**	**10b**

[a] Product ratios (±5%) are based on ^1H NMR spectra. [b] Exhibits marked propensity for allylic rearrangement. [c] Could not be obtained pure but its presence was inferred from high-field NMR data.

The results confirm that even a single electron-withdrawing substituent in the *endo* position is capable of inducing *syn*-facial electrophilic addition, thus reinforcing our earlier observations.[2] There is also no ambiguity about the initial direction of attack of Br^+. Since the nucleophilic attack on the bromonium ion is followed by an elimination to give the olefins **7** and **8**, the loca-

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[**] Computational and financial assistance from the Centre for Development of Advanced Computing (C-DAC), Pune, is gratefully acknowledged. FAK, RNS, BG thank the Council for Scientific and Industrial Research (CSIR/UGC) for research fellowships. We also thank G. Gunasekaran for experimental assistence.

tion of the bromine atom in these products directly reveals the direction of the initial electrophilic attack. Based on the observed product ratios, the charged electrophile Br^+ as well as neutral CCl_2 prefer to approach the *syn* face of **2a** and **2b**.

To delineate the nature of the electronic control of the observed selectivities, we carried out a topographical analysis of the molecular electrostatic potentials of **1a**, **b** and **2a**, **b** at the ab initio level with the 6-31G basis set, using the parallel SCF program INDMOL.[8] In particular, we focused on the MEP minima whose depth generally correlates with electron density. For both series of compounds, the MEPs about the two π faces are unsymmetrical; the (3, +3) critical point on the *anti* face consistently has a more negative value (Table 2). A similar asymmetry computed for **1c** at the PM3 level has been identified as the principal factor determining facial selectivity for the approach of charged electrophiles.[3] However, as the MEP values at the critical points are significantly less negative than those obtained for typical C=C bonds,[9] electrostatic influences are probably not of primary importance in determining the facial selectivities in these compounds.

Table 2. MEP at (3, +3) minimum and electron density at bond critical point (all values in Hartree) [a].

Cmpd. [b]	MEP at critical point		Density at bond critical point	
	syn	*anti*	σ_s	σ_a
1a	−0.0208	−0.0269	0.2096	0.2174
1b	−0.0270	−0.0307	0.2121	0.2165
1c	−0.0129	−0.0202	0.2130	0.2166
1d	−0.0193	−0.0234	0.2112	0.2169
1e	−0.0012	−0.0083	0.2116	0.2172
2a	−0.0174	−0.0222	0.2114	0.2172
2b	−0.0278	−0.0305	0.2109	0.2171

[a] At a critical point of a scalar field f, $\nabla f = 0$. The critical points are classified in terms of the eigenvalues of the Hessian operator. The MEP and bond critical points are (3, +3) and (3, −1) types in the scalar fields. For details of MEP and density topography see Ref. [10]. [b] MNDO optimized geometries. The olefinic units are essentially planar in all the derivatives.

To confirm the potential role of orbital interactions in determining the facial selectivities in these substrates, the unsymmetrical donor abilities of the σ_s and σ_a bonds (see structures **1** and **2**) were characterized in terms of the electron densities at the corresponding bond critical points (Table 2). In all systems with electron-withdrawing groups, the σ_a bond consistently has a greater density. Operation of Cieplak-type orbital interactions[4] would then lead to the observed *syn*-facial selectivity.

Semiempirical MO calculations on the bromonium ion intermediates resulting from **2**, as well as carbene addition transition states, lead to several additional insights (Table 3). Optimization of the bromonium ion intermediates at the PM3 level[11] leads to classical structures, and cyclic forms are not minima.

Table 3. Calculated heats of formation in kcal mol^{-1} of classical intermediates formed by Br^+ additions and transition states for $:CCl_2$ additions to **2**.

Cmpd.	Site of electrophilic attack	Br^+ [a]		$:CCl_2$ [b]	
		syn	*anti*	*syn*	*anti*
2a	C-7	228.64	229.41	91.53	92.37
	C-8	236.29	236.55	93.17	93.21
2b	C-7	109.05	109.26	−23.11	−22.52
	C-8	115.64	115.76	−21.66	−21.65

[a] PM3 method. [b] AM1 method.

The calculations confirm that Br^+ prefers to attack the C7 center, rather than C8 (by 6–7 kcal mol^{-1}), as a less strained tertiary carbocation is formed in the former. The computed *syn*–*anti* energy differences are small. Nevertheless, for both **2a** and **2b**, the ion formed by addition to the *syn* face is consistently more stable, in agreement with the observed facial selectivities. Interestingly, the preference is larger for the ions formed by attack at C7 and not C8, particularly for **2a** [ΔE (*anti*–*syn*) = 0.8 and 0.3 kcal mol^{-1}, respectively)]. Greater unfavorable electrostatic interactions are anticipated between the Br^+ ion at C7 and *syn* face of **2a**. These are evidently overcome by effective orbital stabilization involving the Br-C-7σ* MO and the relatively electron-rich antiperiplanar σ_a bond.

Transition state energies determined with the AM1 procedure[11] for CCl_2 addition to **2** are also consistent with the observed stereoselectivities.[12] Since the least motion pathway for the addition of a carbene to an olefin is a forbidden pathway,[13] the transition structure is highly unsymmetrical. In effect, the carbene forms a bond to one of the olefinic carbon atoms with a C-C-C angle of about 90°. The chlorine atoms are tilted towards the other carbon, which has a planar coordination characteristic of a carbocation. These features have significant consequences for the facial selectivities of **2**. In view of the unsymmetrical nature of the olefins, two sets of first order saddle points, characterized by a closer approach of the carbene to C7 or C8, are obtained for the *syn*- as well as *anti*-facial additions. Interestingly, the energetically favored transition states correspond to CCl_2 attack at C7. As a result, the newly formed C–C bond is more responsive to the unsymmetrical orbital effects from σ_a and σ_s orbitals. Further, as the chlorine atoms are tilted upwards in the corresponding transition states, any contribution from electrostatic interactions from the norbornyl unit are precluded. Overall, a clear preference for *syn*-facial attack results. For the transition states for attack at C8, there is negligible facial selectivity. Orbital effects and electrostatic interactions seem to cancel.[14]

In summary, we have demonstrated a consistent, remote substituent control of the facial selectivities in electrophilic additions to *endo*-substituted 7-isopropylidenenorbornanes. With ab initio and semiempirical MO calculations, it has been clearly shown that the observed preferences are primarily due to orbital effects.

Received: December 17, 1993 [Z 6565 IE]
German version: *Angew. Chem.* **1994**, *106*, 1433

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any symmetry constraints. Stationary points were characterized rigorously by computing vibrational frequencies. Minima have no modes with an imaginary frequency, while transition structures have one and only one vibration with an imaginary frequency.

[12] Optimized structural data for prototypical transition states for CCl_2 addition to ethylene are quite similar at AM1 and ab initio (3–21G) levels [13b]. We have also found that AM1 transition state energetics correctly reproduce the observed facial selectivities in CCl_2 additions to 8-methylenetricyclo-[3.2.1.$0^{2,4}$]octanes reported by R. W. Hoffmann, N. Hauel, B. Landmann, *Chem. Ber.* **1983**, *116*, 389.

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[14] Ab initio calculations (3-21G) on the AM1 transition structures for CCl_2 addition to **2a** support the general conclusions. Total energies [Hartree] for *syn*- and *anti*-facial addition structures: −1429.12927 and −1429.12620 for C7 approach; −1429.12650 and −1429.12433 for C-8 approach, respectively. Thus, the former structures are energetically favored. Further, *syn*-face attack is preferred to a greater extent in the transition structures corresponding to C7 approach (1.9 vs 1.4 kcal mol^{-1} for C8 approach).

Asymmetric Michael Additions to Chiral α,β-Unsaturated Alkoxycarbene Chromium Complexes**

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The Michael reaction is one of the fundamental processes for carbon–carbon bond formation; and significant advances in asymmetric 1,4-conjugate addition reactions, involving chirally modified substrates or a chiral reaction medium, have been achieved.[1] α,β-Unsaturated Fischer carbene complexes, which are increasingly playing an important role in organic synthesis,[2] behave as reactive Michael acceptors. Since the pioneering work by Casey et al. on additions[3] of carbon nucleophiles, several other nucleophiles have been 1,4-added to heteroatom-stabilized alkenyl-[4] and alkynylcarbene[5] complexes with good regioselectivities and diastereoselectivities;[6] but thus far no examples of enantioselective Michael additions to α,β-unsaturated Fischer carbene complexes are known. The asymmetric Michael reactions of chiral prolinol-derived aminocarbene complex anions to cyclic enones have been recently described.[7] We report herein on highly diastereoselective conjugate additions of β-oxygen-functionalized organolithium compounds, alkyllithium reagents, and lithium enolates to chirally modified α,β-unsaturated alkoxycarbenechromium complexes that are readily available in optically pure form.

In a previous report[8] we described the diastereoselective one-pot synthesis of strained tricyclic ethers by reaction of properly substituted β-oxygen-functionalized organolithium compounds with Fischer vinylcarbene complexes. In order to prepare these unusual tricyclic structures as enantiomerically pure compounds

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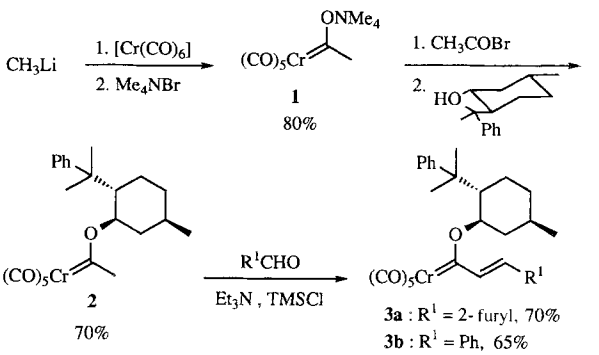
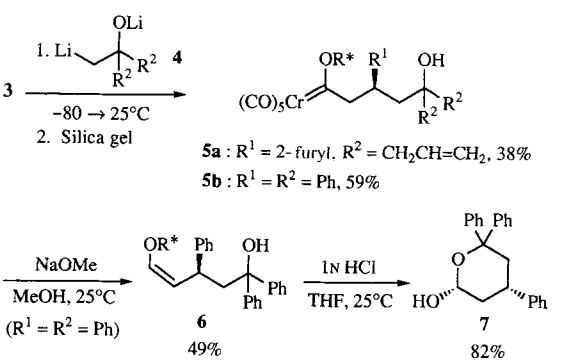
[**] This work was supported by Dirección General de Investigación Científica y Técnica (DGICYT) (Grant PB89-0538). J. M. M. thanks the Ministerio de Educación y Ciencia de España for a doctoral fellowship.



Scheme 1. Synthesis of chiral carbene complexes **3**. TMS = $SiMe_3$.

we synthesized the (−)-8-phenylmenthol-derived vinylcarbenes **3**[9] (Scheme 1). The synthesis of these chiral carbene complexes was achieved starting from the tetramethylammonium complex **1**[10] by alkylation[11] and condensation.[12] The reaction of the organolithium reagent **4**[13] ($R^2 = CH_2{=}CHCH_2$) with the vinylcarbene complex **3a** (R^1 = 2-furyl) led to the acyclic 1,4-addition product **5a** (Scheme 2) with good diastereoselectivity (95% *de*; Table 1, entry 1); but the expected[8] intramolecular



Scheme 2. Asymmetric Michael additions of β-oxygen-substituted organolithium compounds. R*OH = (−)-8-phenylmenthol.

Table 1. Asymmetric Michael additions of organolithium compounds to optically active carbene complexes **3**.

Entry	R^1	R^2	R^3	Product [a]	Yield [%] [b]	*ee* [%]	*de* [c] [%]	$[\alpha]_D$ [d]	Config. [e]
1	2-furyl	allyl	–	**5a**	38	–	95	–	*S*
2	Ph	Ph	–	**7**	82 [f]	87 [g]	–	−137	*S*
3	Ph	Pr	–	**8a**	65	–	95		*S*
4	Ph	Bu	–	**10b**	82 [h]	90 [i]	–	−2.3	*S*
5	Ph	*t*Bu	–	**10c**	88 [h]	80 [i]	–	−9.7	*R*
6	Ph	Me	H	**12a**	55	–	93	–	*S*
7	Ph	Ph	H	**12b**	67	–	97	–	*S*
8	Ph	$(CH_2)_4$		**12c**	69	–	89	–	*R*

[a] Michael adduct used in each case to determine the enantiomeric excess. [b] Yield of isolated product after flash chromatography based on the corresponding carbene complexes **3**. [c] Determined by ^{1}H NMR spectroscopy (300 MHz) and further confirmed by HPLC analysis (Nucleosil 120-10, hexane:THF, 15–36:1). [d] Optical rotations were recorded in CH_2Cl_2 at 20–25 °C, c = 0.25–0.35 g 100 mL^{-1}. [e] Absolute configuration of the new stereogenic center formed in the addition step. Determined by X-ray analyses of compounds **8a** and **12a** (entries 3, 6) and proposed by analogy in all the other adducts assuming the same stereochemical model. [f] Based on enol ether **6**. [g] Determined by HPLC (Chiralcell OD-H, hexane:2-propanol, 3:1) of compound **7** in comparison with the corresponding racemic mixture. [h] Based on the corresponding enol ether **9b**, **9c**. [i] Determined by HPLC (Chiralcell OD-H, hexane:THF, 6–12:1) of 2,4-dinitrophenylhydrazone derivatives of the corresponding aldehydes **10** in comparison with the corresponding racemic products.